

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

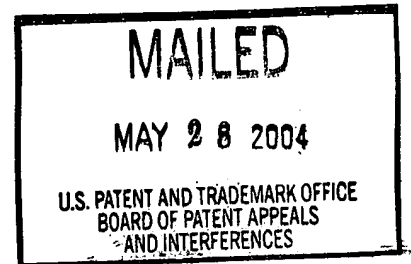
Paper No. 25

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte TAMARA MAES and
TOM GERATS

Appeal No. 2003-1793
Application No. 09/578,361



ON BRIEF

Before SCHEINER, MILLS and GREEN, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-3, 7, 9-11, 19, 20 and 22, which are all of the claims pending in this application.

Claims 1-5, 13 and 19 are illustrative of the claims on appeal and read as follows:

1. A method for simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and flanking sequences, said insertion element flanking sequences originating from a defined population of an organism wherein said gene insertion mutants are to be detected and wherein said insertion element library is built in

a 3D- array of block, row and column pools;

amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

fixing a set of nucleic acid amplification products representing said insertion element flanking sequences derived from said block, row and column pools to a solid support as target for hybridization.

2. The method according to claim 1 wherein the set of nucleic acid amplification products representing said element flanking sequences representing said block, row and column pools are obtained by iPCR using at least one primer or a set of primers based on a sequence of at least one nucleic acid insertion element.

3. The method according to claim 2 wherein said iPCR comprises:
digesting nucleic acid sequences of said block, row and column pools with at least one restriction enzyme resulting in a collection of amplifiable genomic fragments;
ligating at least one amplifiable genomic fragment by self ligation; and
amplifying said at least one amplifiable genomic fragment using a set of internal primers.

4. The method according to claim 3 further comprising reamplifying said at least one amplifiable genomic fragment using at least one primer based on a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements.

5. The method according to claim 1 wherein amplifying insertion element flanking sequences from said insertion element mutant library built in the 3D-array of block, row and column pools comprises amplifying said insertion element flanking sequences using transposon display amplification.

13. A kit for performing the method of claim 1 comprising DNA samples of an insertion element mutant library.

19. A method for parallel simultaneous screening for one or more gene insertion mutants in a population of any organism comprising:

preparing an insertion element mutant library comprising a plurality of nucleic acid insertion elements and insertion element flanking sequences, said insertion element originating from a defined population of an organism wherein said gene insertion mutants are to be detected and wherein said insertion element library is built in a 3D-array of block, row and column pools;

amplifying each of said plurality of insertion element flanking sequences from said insertion element mutant library using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements; and

producing a set of labelled amplification products representing said insertion element flanking sequences derived from said block, row and column pools to use as probes to hybridize to a solid support to which a gene library has been fixed as target(s) for hybridisation, wherein said gene library is organized in at least a two-dimensional array.

The prior art reference relied upon by the examiner is:

Dellaporta 6,013,486 Jan. 11, 2000

Koes et al., (Koes), "Targeted gene inactivation in petunia by PCR-based selection of transposon insertion mutants," PNAS USA, Vol. 92, pp. 8149-8153 (1995)

Souer et al., (Souer), "A general method to isolate genes tagged by a high copy number transposable element," The Plant Journal, Vol. 7, No. 4, pp. 677-685 (1995)

Vos et al, (Vos), "AFLP: A new technique for DNA fingerprinting," Nucl. Acids. Res., Vol. 23, NO. 21, pp. 4407-4414 (1995)

Grounds of Rejection

1. Claims 1-3, 7, 9-11, 19, 20 and 22 stand rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes.

2. Claims 13-17 and 21 also stand rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes.

3. Claims 4 stands rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Souer.

Appeal No. 2003-1793
Application No. 09/578,361

4. Claims 5, 6, 8 and 12 stand rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Vos.

We affirm these rejections.

Claim Grouping

According to appellants, the claims do not stand or fall together. (Brief, page 4). Appellants group the claims in the following groups. Group 1, claims 1-3, 7, 9-11, 20 and 22; Group 2, claim 4, Group III, claims 5, 6, 8 and 12; Group IV, claims 13-17; and Group V, claims 19 and 21. Since the individual claims of each separate group are not argued, we decide this appeal with respect to the prior art rejection on the basis of claim Group 1, claim 1; Group II, claim 4; Group III, claim 5; Group IV, claim 13 and Group V, claim 19. 37 CFR §1.192(c)(7) (1998).

DISCUSSION

35 U.S.C. § 103

1. Claims 1-3, 7, 9-11, 19, 20 and 22 stand rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes.

In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. See In re Rijckaert, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). It is well-established that the conclusion that the claimed subject matter is prima facie obvious must be supported by

Appeal No. 2003-1793
Application No. 09/578,361

evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention.

See In re Fine, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988).

It is the examiner's position that Dellaporta teaches each of the claim elements except "Dellaporta teaches forming pools of DNA but does not teach 30 DNA samples from 100 plants each, wherein the DNA from 100 plants is distributed into a 3D array of 10 blocks, 10 rows, and 10 columns." Answer, page 5.

According to the examiner, Dellaporta describes "[p]ools containing DNA from different combinations of individuals, designed in such a way that sequences representing single members of a population can be identified without the need to analyze each member individually. For example, pools can be distributed into a 2X2 grid, comprising rows and columns. (col. 3, lines 58-65; col. 15, lines 58-67)." Answer, page 5.

To make up for the failure of Dellaporta to describe a 3D array as required by claim 1, the examiner relies on Koes. According to the examiner, Koes describes "a method of preparing an insertion element mutant library of transposable elements dTph1 in petunia plants. They describe pooling plant material from three sets of 1,000 plants each in patterns of blocks, rows and columns, e.g. 10 blocks, 10 rows, 12 columns (page 8150, col. 2, par. 4,5; Fig. 2, 3)." Id.

The examiner concludes (Id.):

It would have been obvious to one of ordinary skill in the art at the time of the invention to have used the DNA pooling method of Koes et al. in the insertion element library screening method of Dellaporta. The motivation to do so, expressly provided by Koes et al., would have been that three dimensional was less laborious (single round of screening), less liable to detect false positives and identified single plants directly.

Appellants respond to the examiner's position, arguing that the cited references fail to teach each and every limitation of independent claim 1 and therefore do not render the claims of the present invention obvious. Brief, page 6. Appellants agree with the examiner that "Dellaporta does not teach ... an insertion element library built into a 3D block, row and column pools..." Id. However, appellants argue that the combination of Dellaporta and Koes is improper and thus Koes does not make up for the deficiencies of Dellaporta.

For the reasons herein, we do not find appellants arguments of record to be persuasive rebuttal in response to the examiner's prima facie case of obviousness. In particular, we agree with the examiner Koes provides a reason, suggestion or motivation to substitute the 3D array of block, row and column pools for the 2X2 grid in the method of selection of insertion mutants of Dellaporta. Koes states that the three dimensional array is less laborious, provides for a single round of screening, and is less liable to detect false positives and identified single plants directly. Koes, page 8152, Column 1.

Furthermore, we disagree with appellant that "Dellaporta teaches away from Koes []." Brief, page 7. Appellants argue that "[a]s stated in Dellaporta, mutant identification systems where 'transposon-induced [sic] mutations are isolated from known gene sequences by the general strategy known as 'site-selected' mutagenesis...rel[ying] on the power of PCR to amplify a collection of specific junction fragments between an inserted element and a known target gene sequence ... have had limited success in applications toward large scale genomic investigations." Brief, page 8.

The examiner responds to this argument indicating that "Koes [] is relied upon for the teaching of a 3D pooling technique, not for the amplification method, whereas Dellaporta is relied on for teaching of the amplification of insertion junctions." Answer, page 12. In other words, the examiner essentially argues, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references." In re Merck & Co., Inc., 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986). Instead, the test of obviousness is "whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art. See In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991) and In re Keller, 642 F.2d 413, 425, 208 USPQ 871, 881 (CCPA 1981). Moreover, in evaluating such references it is proper to take into account not only the specific teachings of the references but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. In re Preda, 401 F.2d 825, 826, 159 USPQ 342, 344 (CCPA 1968).

We agree with the examiner, that given the teaching in the prior art of the advantages of using a 3D block pooling technique for insertional mutant studies, it would have been obvious to one of ordinary skill in the art to substitute the 3D block of Koes for the 2x2 grid of Dellaporta. We do not agree with appellants that one of ordinary skill in the art would be discouraged from using the more efficient 3D block of Koes in place of the 2x2 grid of Dellaporta in a method of selection of insertion mutants in view of the disclosures of Dellaporta and Koes. While one of ordinary skill in the art may have been discouraged or led away from using a site directed mutagenesis technique in an insertional mutant assay in view of the disclosure of Koes, the examiner does not rely on Koes for this teaching. In our view, the examiner has provided sufficient motivation to use the more efficient 3D block array of Koes in place of the 2x2 grid of Dellaporta in a method of selection of insertion mutants, notwithstanding any comments in Koes regarding the site-directed mutagenesis technique. We find no teaching away from substitution of a more efficient 3D block array in view of the

disclosure of Koes.

Appellants additionally argue that Dellaporta fails to disclose a step of “amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools,’ as presently claimed...” Brief, page 6. Appellants argue that “the amplification methods in Dellaporta are limited to ‘using a single primer set [that] may amplify a representative sample of insertion junctions from a particular group of individuals” and that “Dellaporta does not amplify **all** of the insertion element flanking sequences in the insertion element mutant library”. [Emphasis in original.] Brief, page 6.

In order to address appellant’s argument, we need to review the scope of claim 1 before us. Claim 1 recites a step of “amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements.” Dependent claim 2 recites that the amplification products representing the insertion element flanking sequences are “obtained by iPCR using at least one primer or a set of primers based on a sequence of at least one nucleic acid insertion element.” [Emphasis added.]

Thus, it would reasonably appear that claim 1, through application of the doctrine of claim differentiation, encompasses the use of a single primer set, such as that disclosed in Dellaporta at column 12, lines 6-8, to amplify each of a plurality of insertion element flanking sequences. Dellaporta describes in column 11, lines 41-62, that either non-selective or selective amplification of insertion junctions may be performed.

Dellaporta further indicates the “[i]nverse polymerase chain reaction (IPCR) ... permits the amplification of regions that flank any DNA segment of known sequence...”

Therefore, in our view, Dellaporta describes the selective amplification of each of a plurality of insertion element flanking sequences (i.e., multiple insertion element flanking sequences in a 2x2 grid) when the insertion element flanking sequence is chosen to amplify each of a single known sequence. See also Dellaporta, example 7, columns 30-31.

Similarly, the claim 1 language does not exclude the use of a primer set including different primers which amplify different insertional mutants in a sample, as long as each insertion element is amplified by a primer. This becomes clear when claim 1 is interpreted in view of the claim 2 indication that at least one primer or a set of primers based on a sequence of at least one nucleic acid insertion element may be used.

With respect to claim 19, appellants repeat arguments that the cited references to not teach a 3D array or a step of “amplifying each of said plurality of insertion element flanking sequences from said block, row and column pools using at least one primer derived from a sequence of a nucleic acid insertion element of said plurality of nucleic acid insertion elements.” Brief, page 12. These arguments have been previously addressed and have not been found convincing.

We find no argument of appellants of record as to interpretation of the claim language which is contrary to the interpretation provided herein. We agree with the examiner that the evidence presented supports a prima facie case of obviousness of the claims, as interpreted herein. We do not find the appellants have presented sufficient argument or evidence to rebut the examiner's prima facie case. The rejection of claims 1-3, 7, 9-11, 19, 20 and 22 for obviousness is affirmed.

2. Claims 13-17 and 21 also stand rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes.

With respect to claim 13, the examiner argues that the reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time of the invention.

Appellants merely argue neither Dellaporta or Koes motivate the use of a kit. Brief, page 11. The examiner responds, arguing that "one of the methods for genetic characterization of insertional mutants Dellaporta considers [is] chip-based technologies, in which high densities of oligonucleotides are fixed to a solid support." "Gene chips were commercially available from 'Affymetrix' since 1994 and provided efficient economical gene analysis tools, since each collection of DNA fragments on a chip could be repeatedly hybridized with different sets of probes, and large numbers of DNA fragments could be probed simultaneously." Answer, page 22. The examiner argues that such is evidence that reagent kits for performing DNA detection assays

were conventional in the field of molecular biology at the time of the invention.

Therefore, the examiner concludes "it would have been obvious to one of ordinary skill in the art at the time of the invention to have packaged the insertion element mutant library and amplified insertion element flanking sequences into a kit for the expected benefits of convenience and cost-effectiveness for practitioners in the art wishing to perform screening for insertion mutants." Answer, pages 8-9.

We do not find appellants have presented sufficient evidence or argument in rebuttal to the examiner's prima facie case of obviousness. Appellants do not respond to the examiner's argument and evidence (Dellaporta) that reagent kits for performing DNA detection assays were conventional in the field of molecular biology at the time of the invention. The rejection of claims 13-17 for obviousness is affirmed.

3. Claim 4 stands rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Souer.

The examiner acknowledges that neither Dellaporta nor Koes teach "reamplifying at least one amplifiable genomic fragment" as set forth in claim 4. Answer, page 6. However, the examiner finds that "Souer [] teach a method of isolation gene insertion mutants in petunia plants based on the amplification of insertion element dTph1 flanking sequences using a combination of iPCR and differential screening of amplification products..." Id. According to the examiner Souer teaches that "[a]mplificaton yield can be improved by using re-amplification with nested primers

Appeal No. 2003-1793
Application No. 09/578,361

complementary to the insertion element." [Emphasis in original.] Answer, page 6, Souer, page 680, col. 1.

Appellants argue that a prima facie case of obviousness has not been established by the examiner because, "Souer [] does not suggest or motivate amplifying each of the plurality of insertion flanking sequences from the block, row and column pools." Brief, page 9. Appellants also argue that the level of skill in the art cannot be relied upon to provide the suggestion to combine references, citing Al-Site Corp. v. VSI Int'l Inc., 174 F.3d 1308, 50 USPQ 2d 1161 (Fed. Cir. 1999). Id.

The examiner points out, in response, that Dellaporta stresses the fact that rapid and efficient method of identification of large numbers of insertional mutants are necessary and provides such a method. The examiner argues that improved amplification yield provides sufficient material for formation of the insertion junction arrays and improved amplification specificity reduces the number of false positive screening results leading to the identification of potentially useful plants with the minimum of time and expense (Souer, page 683; Koes, page 8152). Answer, page 16. The examiner concludes the motivation is provided by Souer and not the level of skill in the art. Id.

Appellants' reliance on Al-Site is not well-taken. We agree with Appellants that the "level of skill in the art [alone] can never act as a bridge over gaps in substantive presentation of an obviousness case..." Al-Site, at 1171. However, in the present case we find no gaps in the examiner's prima facie case and do not find that the examiner

Appeal No. 2003-1793
Application No. 09/578,361

improperly relies on the level of skill in the art. The art cited by the examiner is relevant evidence of advances in the field of endeavor, as they relate to improved techniques for screening mutants, including gene insertion mutants.

We do not find the appellants have provided sufficient rebuttal to the examiner's prima facie case of obviousness. In view of the above, the rejection of claim 4 under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Souer is affirmed.

4. Claims 5, 6, 8 and 12 stand rejected under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Vos.

The examiner acknowledges in the Answer that neither Dellaporta nor Koes teach amplification by transposon display amplification. Answer, page 7. Vos is relied on for the disclosure of a DNA fingerprinting technique which uses transposon display amplification. The method amplifies restriction fragments using primers complementary to the adaptors and restriction site sequences. Answer, page 9. According to the examiner and Vos, "[t]he fragments could be subjected to a second round of amplification using modified primers. The amplified fragments can be selected by using a biotinylated adaptor for the hexacutter and separated from the rest of the fragments with streptavidin beads". The examiner concludes, "it would have been obvious to one of ordinary skill in the art at the time of the invention to have used the DNA amplification method of Vos [] with the library of gene insertion mutants of Dellaporta and Koes []. The motivation to do so, expressly provided by Vos [], would have been that

amplification and isolation of DNA fragments was achieved without the prior knowledge of their sequences." Answer, page 8.

Appellants argue that "Vos [] does not disclose or suggest transposon [sic] display amplification but rather Vos[] teaches a DNA fingerprinting technique called AFLP." Brief, page 10. Appellants argue that Vos does not amplify insertion element flanking sequences from the insertion element mutant library. Id.

Appellants argue that the amplification and reamplification steps of claims [5 and] 6 require primers based on a sequence of the insertion element, while the primers of Vos are generic. Brief, pages 10-11. Appellants conclude that, "one of skill in the art would not have a reasonable expectation of success by combining the AFLP method of Vos [] with the screening methods disclosed in Dellaporta and Koes []." Brief, page 11.

The examiner relies on Vos for its transposon display amplification method and its use of primers, while relying on Dellaporta and Koes for the insertion element mutant library techniques. The examiner replies to appellants, that the primers [of Vos] consist of three parts: a core sequence, an enzyme specific sequence (which together are complementary to the adaptor sequence) and a selective extension, which is complementary to the genomic sequence." Answer, page 19: Thus, the primers of Vos are not generic in a sense that they contain a region complementary to the genomic sequence enclosed between the adapters, which allows selective amplification of subsets of sequences. Id.

Appeal No. 2003-1793
Application No. 09/578,361

In view of the above, we are not persuaded by appellants' arguments with respect to Vos teaching generic primers. We agree that the examiner has provided a sufficient reason, suggestion or motivation to combine Vos with Dellaporta and Koes, and that the examiner has set forth a prima facie case of obviousness. We do not find appellants have provided sufficient argument or evidence to rebut the examiner's prima facie case of obviousness. The rejection of the claims 5, 6, 8 and 12 for obviousness is affirmed.

CONCLUSION

The rejection of claims 1-3, 7, 9-11, 19, 20 and 22 under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes is affirmed.

The rejection of claims 13-17 and 21 under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes is affirmed.

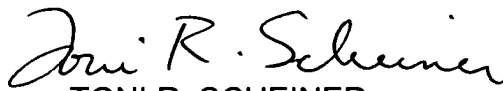
The rejection of claim 4 under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Souer is affirmed.

The rejection of claims 5, 6, 8 and 12 under 35 U.S.C. 103(a) for obviousness over Dellaporta in view of Koes and Vos is affirmed.

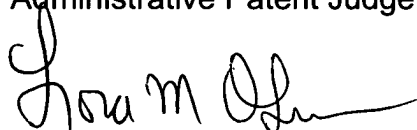
Appeal No. 2003-1793
Application No. 09/578,361

No time period for taking any subsequent action in connection with this appeal
may be extended under 37 CFR § 1.136(a).

AFFIRMED


TONI R. SCHEINER
Administrative Patent Judge


DEMETRA J. MILLS
Administrative Patent Judge


LORA M. GREEN
Administrative Patent Judge

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Appeal No. 2003-1793
Application No. 09/578,361

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